Long-term assessment of patients with acute hepatic porphyria who were not attack-free after 6 months of givosiran treatment: a post hoc subgroup analysis of the phase 3 ENVISION study[1]

1 Introduction

What is AHP?[2,3]

- Acute hepatic porphyria (AHP) is a group of four rare, genetic, multisystemic disorders caused by defects in the heme biosynthesis pathway
- AHP can be potentially progressive with long-term complications

- A build-up of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) in the body can cause:
  - **Attacks**
    - Appear suddenly and are short lived
    - May be recurrent or non-recurrent
    - Severe and debilitating symptoms
  - **Chronic symptoms**
    - Appear more slowly and can last a long time
    - Negatively affect day-to-day activities and quality of life

Symptoms of AHP[4,5]

- Pain
- Headache
- Seizures
- Photosensitivity

- Nausea
- Vomiting
- Constipation
- Diarrhea

- Muscle weakness
- Paralysis
- Sensory loss
- Tachycardia

- Insomnia
- Fatigue
- Anxiety
- Depression
- Memory loss
- Confusion

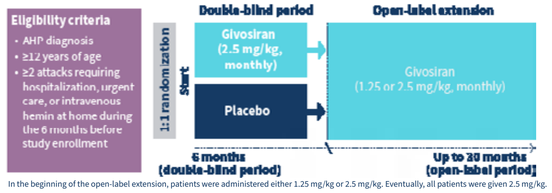
These are not all the possible signs and symptoms of AHP

What is givosiran?

- An RNAi therapy that is used to treat adults with AHP[6]
- Please see the GIVLAARI full prescribing information for the FDA-approved product labeling[5]

What was the ENVISION study?

- ENVISION (NCT03338816) was a randomized, double-blind, placebo-controlled, multinational phase 3 study in adult patients with AHP (N=94), with a 30-month open-label extension (OLE) period (N=93)[7,8]
  - During the 6-month double-blind period, efficacy was measured as the rate of AHP attacks requiring hospitalization, urgent healthcare visit, or intravenous (IV) hemin administration at home
  - Long-term efficacy and safety of givosiran treatment was evaluated through the OLE period



In the beginning of the open-label extension, patients were administered either 1.25 mg/kg or 2.5 mg/kg. Eventually, all patients were given 2.5 mg/kg.

What is this post hoc analysis?

- This descriptive post hoc subgroup analysis of patients who were either attack-free or not attack-free after 6 months of givosiran treatment describes the long-term outcomes up to month 36, which include[1]:
  - annualized attack rate (AAR)
  - urinary ALA and PBG concentrations
  - EQ visual analog scale (EQ-VAS) score
  - 12-item short-form health survey (SF-12) version 2 physical component summary (PCS) score
- In a post hoc descriptive analysis composed of patients who had completed the double-blind and open-label periods, patients were grouped into:[1]

Attack-Free: had no attacks after 6 months of givosiran treatment (46 patients)

Not Attack-Free: had at least 1 attack after 6 months of givosiran treatment (33 patients)

All Patients: Attack-Free and Not Attack-Free groups combined (79 patients)

The listed endpoints were assessed as exploratory endpoints during the 36 month duration of the ENVISION study as part of the pre-specified analysis.

2 Methods

Annualized attack rate[1]

Methods

- AAR was defined as the average number of attacks per person in a year that required any of the following:

Hospitalization | **Urgent care visit** | **Intravenous hemin at home**

- The AAR was calculated every 6 months to illustrate how the AAR changes throughout each 6-month period from the historical AAR baseline through to month 36
- Historical AAR was defined as the composite of porphyria attacks requiring hospitalization, an urgent healthcare visit, or intravenous hemin administration at home during the 6 months before randomization

ALA and PBG urine concentrations[1]

Methods

- To estimate effect of givosiran, concentrations of ALA and PBG in urine were:
  - measured throughout the study
  - compared with starting values

Health-related quality of life (HRQoL)[1]

HRQoL was measured using:

- EQ-VAS score
  - Rated[9] on a scale of 0 to 100 (worst to best health you can imagine)
  - An increase of more than 7-8 EQ-VAS points has been considered as 'clinically meaningful' in other chronic diseases[9,10]
- SF-12 PCS score
  - General health, current effect of health on activities, and effect of physical health or pain on work or activities in the past 4 weeks were scored[11,12]

3 Results

Baseline demographics and disease characteristics[1]

Demographic/characteristic	Attack-Free (n=46)	Not Attack-Free (n=33)	All patients treated with givosiran (N=79)
Age at screening, years, median (min, max)	41.5 (19.0, 61.0)	36.0 (20.0, 57.0)	38.0 (19.0, 61.0)
Time since diagnosis, years, mean (SD)	9.43 (10.00)	10.32 (9.92)	9.80 (9.91)
Age at diagnosis, years, mean (SD)	32.44 (11.39)	26.70 (9.03)	30.04 (10.79)
Female, n (%)	39 (84.8)	31 (93.9)	70 (88.6)
Prior hemin prophylaxis regimen, n (%)	18 (39.1)	13 (39.4)	31 (39.2)
Prior chronic symptoms when not having attacks, n (%)	23 (50.0)	20 (60.6)	43 (54.4)

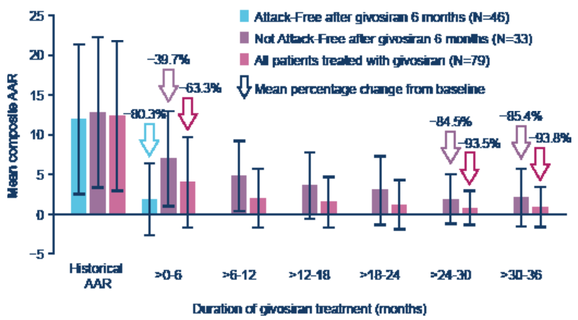
Annualized attack rate[1,14]

The proportion of patients who became attack-free increased over time

- In the Not Attack-Free group, the percentage of patients who became attack-free changed from 9% (3/33 patients) after >6-12 months of treatment to 79% (26/33 patients) after >30-36 months of treatment
- In the Attack-Free group, all patients remained attack-free throughout the 36 months of the study

Mean composite AAR decreased over time with givosiran treatment

- 1st 6 months of treatment: mean composite AAR was reduced in all groups relative to historical AAR
- After 1st 6 months of treatment: Attack-Free group had no attacks and Not Attack-Free group had reduced attacks over 36 months of givosiran treatment

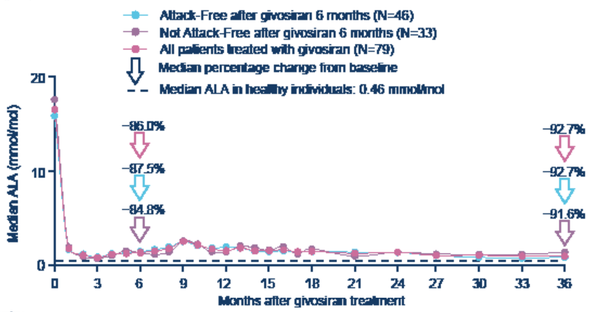


No. of patients:							
Attack-free	46	46			46	23	
Not attack-free	33	33			33	17	
Total	79	79			79	40	

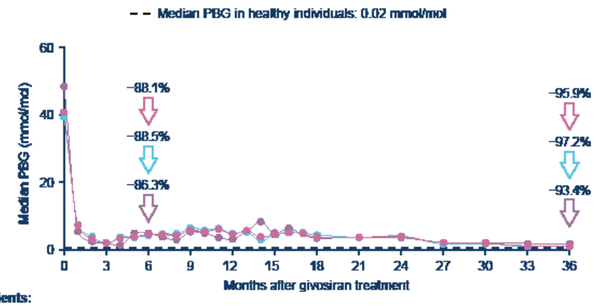
ALA and PBG urine concentrations[1]

The reduction of median urinary ALA and PBG concentrations were sustained over time with givosiran treatment

- ALA and PBG reductions of >90% were observed through 36 months of givosiran treatment in the Not Attack-Free and Attack-Free groups*



No. of patients:													
Attack-free	46	46	46	46	45	45	45	43	43	45	45	22	24
Not attack-free	33	32	31	33	31	32	33	32	31	33	31	16	16
Total	79	78	77	79	76	77	78	75	74	78	76	38	40



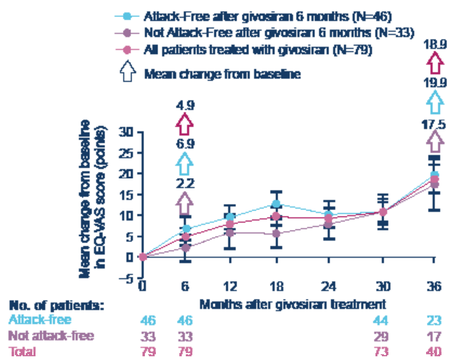
No. of patients:													
Attack-free	46	46	46	46	45	45	45	43	43	45	45	22	24
Not attack-free	33	32	31	33	31	32	33	32	31	32	31	16	16
Total	79	78	77	79	76	77	78	75	74	77	76	38	40

*Baseline was redefined relative to the first dose of givosiran for patients receiving placebo in the DB period and analysis visits mapped based on redefined baseline.

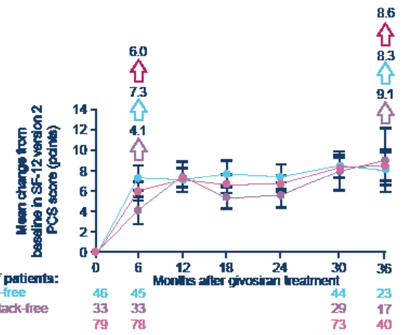
Health-related quality of life (HRQoL)[1]

HRQoL scores inceased over time with givosiran treatment

- HRQoL scores increased in all patients*
  - After 6 months of treatment (0 months vs 6 months)
  - After 36 months of treatment (0 months vs 36 months)
    - At 36 months, EQ-VAS and SF-12 PCS score increases of >17.5 and >8, respectively, were observed in the Not Attack-Free and Attack-Free groups



No. of patients:						
Attack-free	46	46			44	23
Not attack-free	33	33			29	17
Total	79	79			73	40



No. of patients:						
Attack-free	46	45			44	23
Not attack-free	33	33			29	17
Total	79	78			73	40

*Baseline was redefined relative to the first dose of givosiran for patients receiving placebo in the DB period and analysis visits mapped based on redefined baseline.

Safety[1]

- In the 6-month double-blind placebo-controlled period of ENVISION, at least 1 adverse event was experienced in 90% of patients treated with givosiran (n=48) and 80% of patients receiving placebo (n=46)[7]
  - During this period, the most frequently occurring adverse events in patients treated with givosiran were nausea and injection site reactions
- Throughout the 36-month study period of ENVISION, including the 30-month OLE, 97% of the 94 patients treated with givosiran experienced any adverse event[8]
  - The most frequently reported adverse events occurring in ≥20% of patients were injection site reactions, nausea, fatigue, nasopharyngitis, headache, urinary tract infection, and upper respiratory tract infection
  - Hepatic and renal adverse events were reported in 18 (19%) and 21 (22%) patients, respectively
  - Increased blood homocysteine was reported in 15 (16%) patients; 2 of these events were considered serious
  - Pancreatitis was reported in 1 patient

Patients with ≥1 event, n (%)	All patients treated with givosiran (N=94)
Serious AE	37 (39)
Severe AE	35 (37)
AE leading to treatment discontinuation	6 (6)
AE leading to study withdrawal	4 (4)
Death	0

Study Limitations[1]

- This post-hoc analysis was exploratory in nature and no formal statistical testing was planned for this analysis and, therefore, no statistical conclusions can be drawn
  - This analysis was not designed to evaluate the differences between and within group
  - Safety was not assessed in this post hoc analysis
- The study is limited by the relatively small number of patients in the study population
- For each outcome, there is a drop in patient numbers from 30 months to 36 months, as the data presented are only available for how long the patients were on givosiran therapy
- SF-12
  - Includes concepts that may not be relevant for the target population (ie, general health, moderate activities, climbing stairs)
  - The domains of bodily pain, social functioning, role limitations due to physical problems, and general health contribute more to the total PCS score
- EQ-VAS[13]
  - Includes measurement properties that were assessed for a broadly defined population
  - Self-completion may introduce possibly confounding effects

4 Summary

- **In patients who remained attack-free and those who did not remain attack-free after 6 months of givosiran treatment, the data from the 36-month ENVISION post hoc analysis suggest decreased AAR, decreased urinary ALA/PBG concentrations, and increased SF-12 PCS and EQ-VAS scores with givosiran treatment through to the end of study[1]**

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